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(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING STABILISED AMORPHOUS FORM OF DONEPEZIL HYDROCHLORIDE

(57) Abstract: The present invention relates to stabilised pharmaceutical compositions with an amorphous form of 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methyl-piperidine (donepezil) hydrochloride and to a process for the stabilisation of this compound. The pharmaceutical composition is prepared by in situ formation of donepezil hydrochloride and loading the obtained solution onto a mixture of pharmaceutically acceptable excipients. The amorphous form of donepezil hydrochloride is stabilised by adding a crystallization inhibitor to the solution or to the mixture of pharmaceutically acceptable excipients.

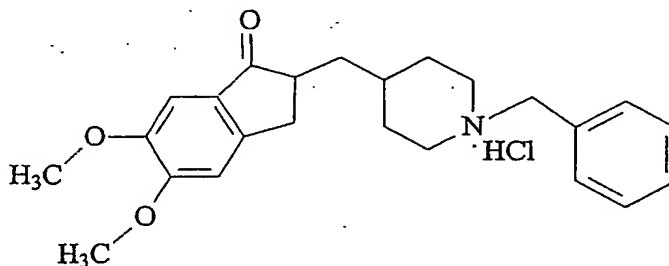
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PHARMACEUTICAL COMPOSITION CONTAINING STABILISED AMORPHOUS FORM OF DONEPEZIL HYDROCHLORIDE

The present invention relates to a stable pharmaceutical composition containing 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methyl-piperidine (donepezil) hydrochloride and to a method for the stabilisation of this compound.

Technical Field of the Invention

Donepezil hydrochloride is a well-known medicinal active ingredient with a strong and highly selective acetylcholinesterase inhibition and is identified by the following chemical formula:



Donepezil is described to be effective in the treatment and/or prevention of various diseases such as senile dementia, particularly senile dementia of Alzheimer's type, cerebrovascular diseases accompanying cerebral apoplexy, e.g. cerebral haemorrhages or cerebral infarct, cerebral arteriosclerosis, head injuries and other diseases. It is also used in the treatment and/or prevention of aprosexia, speech disorders, hypobulia, mood changes, attention deficit hyperactivity disorders, recent memory disturbances, hallucinatory-paranoid syndrome, behaviour changes and other similar diseases accompanying encephalitis, cerebral palsy and others.

Prior Art

Various processes for the synthesis of donepezil and/or compositions with donepezil as a medicinal active ingredient have been described.

WO 97/46527 describes a method for the preparation of polymorphs I-V and of an amorphous form of donepezil hydrochloride. The amorphous form is prepared in such a way that donepezil hydrochloride is dissolved in water, the solution is cooled to a low temperature and freeze-dried for 4 days at the temperature -82°C . When comparing the results of stability testing it was established that the polymorphs I-IV are preferred over the amorphous form because they show enhanced chemical stability. Thus, the amorphous form is less stable when compared with the polymorphs I-IV. After a three-week exposure to the temperature of 80°C , the content of impurities rose from 0.12% at time 0 (zero) to 3.29%. Further, in hygroscopicity testing it was found that the amorphous form is significantly more hygroscopic when exposed to different relative humidities as compared to polymorphs I-IV. At the exposure of the amorphous form to a 100.0 % relative humidity, the water content rose from initial 2.03% to 15.44%.

EP-A-1 086 706 describes the preparation of donepezil in salt form to enhance stability. In order to achieve a higher stability the use of organic acids is suggested to be preferred over hydrochloric acid, since the use of the latter yields a higher amount of impurities. When 5 mg of hydrochloric acid were added to 5 mg/5 ml of donepezil solution and it was stored at 60°C for one month, the ratio of the area of impurities on the chromatogram was 0.42%. In a second experiment, wherein 5 mg of hydrochloric acid were added to 5 mg/5 ml of donepezil solution containing 10% of povidone and stored at the same conditions (60°C , one month), the ratio of the area of impurities on a chromatogram was 2.45%.

EP-A-1 120 109 describes the use of steam-extruded polymers for enhancing the disintegration and dissolution of a pharmaceutical composition. Although an amorphous form is described in this document, the rapid disintegration was achieved by the use of steam-extruded polymers.

According to the literature data, amorphous forms are generally more hygroscopic and less stable than crystalline forms and crystallize into a crystalline form or a mixture of crystalline forms (Brittain HG. Polymorphism in Pharmaceutical Solids. 1st ed. New York: Marcel Dekker, 1999). Amorphous substances may be stabilised by the addition of crystallization inhibitors (Chem. Pharm. Bull. 1983; 31 (7): 2510-2512).

Technical Problem

Considering all the facts described in the prior art, there existed a need to prepare a stable formulation containing the amorphous form of donepezil hydrochloride. This problem was solved by preparing donepezil hydrochloride *in situ* and stabilizing the amorphous form by the addition of a crystallization inhibitor.

Detailed Description of the Invention

An object of the present invention is a pharmaceutical composition containing amorphous or stabilised amorphous donepezil hydrochloride, which composition is obtained by preparing donepezil hydrochloride *in situ* and by adding a crystallization inhibitor.

A process for the preparation of a pharmaceutical composition containing donepezil hydrochloride comprises the following steps:

- a) dispersing donepezil in a pharmaceutically acceptable solvent and adding a hydrochloric acid solution to the dispersion,

or. *vice versa*, adding donepezil to a hydrochloric acid solution in a pharmaceutically acceptable solvent, and

- b) loading the obtained solution onto a mixture of pharmaceutically acceptable carriers.

The crystallization inhibitor/s can be added either to the solution obtained under a) or to the mixture of pharmaceutically acceptable carriers under b).

A further object of the present invention is the preparation of the amorphous form of donepezil hydrochloride by spray-drying a donepezil hydrochloride solution. The solution of donepezil hydrochloride can be prepared either *in situ* by adding a hydrochloric acid solution to a dispersion of donepezil, or *vice versa*, by dissolving donepezil in hydrochloric acid or by dissolving donepezil hydrochloride in a pharmaceutically acceptable solvent or a mixture of solvents.

Optionally, the amorphous form of donepezil hydrochloride can be stabilised by dissolving a crystallization inhibitor in a solution of donepezil hydrochloride, whereupon the solvent is removed by spray-drying. Subsequently, the amorphous form or the stabilised amorphous form of donepezil hydrochloride can be dissolved in a pharmaceutically acceptable solvent and further processed by loading the obtained solution onto a mixture of pharmaceutically acceptable excipients. The dry amorphous form or the stabilised dry amorphous form of donepezil hydrochloride can be admixed to pharmaceutically acceptable excipients so as to prepare a pharmaceutical composition.

The solution of donepezil hydrochloride prepared *in situ* or by dissolving the amorphous form or the stabilised amorphous form of donepezil hydrochloride, can be loaded onto pharmaceutically acceptable carriers such as a powdered mixture of excipients, pellets, crystals, granules (e.g. granulated excipients), microtablets, tablets.

The final pharmaceutical dosage forms can be formulated by known methods such as wet or dry granulation, direct tableting, pelletisation.

The conventional equipment used for manufacturing pharmaceutical compositions can be a high shear mixer/granulator, Wurster coating system, fluid bed granulator (top spray, bottom spray, tangential spray), conventional coating pans etc.

The pharmaceutical composition can be in any conventional pharmaceutical unit dosage form such as granules, pellets, tablets, film-coated tablets, fast dispersible tablets, capsules etc.

According to the present invention, the crystallization inhibitor is selected from at least one of cellulose derivatives, polyvinylpyrrolidone and derivatives thereof, xanthan gums, pectins, alginates, tragacanth and derivatives, gum arabic and derivatives, carrageenans, agar and derivatives, polysaccharides from microbiological sources, arabinogalactanes, galactomannans, dextrans and the like. The preferred crystallization inhibitors are cellulose derivatives and polyvinylpyrrolidone and its derivatives.

The crystallization inhibitor is added in an amount from 0.0001 g to 5.0 g for 1 g of donepezil hydrochloride, preferably between 0.5 g to 2.0 g.

The solution is prepared by the addition of donepezil to hydrochloric acid in a molar ratio of 1 : 0.5-5, preferably in a molar ratio of 1:0.5-3. The pH value of the solution obtained is between 2 and 6, preferably between 3.0 to 5.5.

The pharmaceutically acceptable solvents are water, a mixture of water with water-miscible solvents, acetone, alcohols such as ethanol, methanol, isopropanol, preferably water or a mixture of water with alcohols, or alcohols.

The pharmaceutically acceptable excipients can be diluents such as microcrystalline cellulose, lactose (anhydrous or in monohydrate form), other sugars such as mannitol, saccharose or a mixture thereof, siliconised microcrystalline cellulose, calcium hydrogen phosphate; binders such as povidone, microcrystalline cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hypromellose, starch, pregelatinised starch; disintegrants such as maize starch, sodium starch glycolate, crospovidone, microcrystalline cellulose, carboxymethylcellulose sodium, Amberlite®; lubricants such as magnesium stearate, calcium stearate, sodium laurylsulphate, hydrogenated vegetable oil, hydrogenated castor oil, sodium stearyl fumarate.

The method according to the present invention is advantageous over the known prior art in that, unexpectedly and surprisingly, a highly stable amorphous form of donepezil hydrochloride with a low content of impurities in the pharmaceutical composition is obtained. The results of the stability testing of the pharmaceutical compositions with the amorphous form according to the present invention are presented in Table 1.

Table 1

Time of exposure to air at 40°C/75% RH; (days)	Total amount of related substances (%)
0	0.05
28	0.09

The present invention is illustrated by the following Examples without being limited thereto.

Example 1

Preparation of tablets

Donepezil (20 g) was dispersed in a pre-prepared aqueous solution (240 ml) containing concentrated hydrochloric acid (4 ml) and povidone (20 g). Lactose monohydrate (294 g), microcrystalline cellulose (200 g), maize starch (30 g) and hydroxyethylcellulose (15 g) were passed through a 30-mesh sieve and subsequently mixed in a fluid bed granulator.

The aqueous solution of donepezil hydrochloride to be granulated was sprayed onto the powder mixture in the fluid-bed granulator and after the completed spraying the obtained granulate was dried in a fluid-bed dryer at an inlet temperature of 60°C. The dried granulate was passed through an 18-mesh sieve and mixed with maize starch (30 g) and magnesium stearate (3 g) in a biconic mixer.

The mixture to be tableted (the granulate with added maize starch and magnesium stearate) was compressed into tablets, each containing 5 mg of donepezil hydrochloride. The average weight of the tablets was 140 mg.

Example 2

Preparation of tablets

Donepezil (20 g) was dispersed in a pre-prepared aqueous solution (240 ml) containing 0.5 M hydrochloric acid (35 ml). The thus prepared aqueous solution of donepezil hydrochloride was admixed with an aqueous solution containing hypromellose (10 g). Microcrystalline cellulose (262 g), lactose monohydrate (262 g) and maize starch (25 g) were passed through a 30-mesh sieve and subsequently mixed in a fluid-bed granulator.

The aqueous solution of donepezil hydrochloride was sprayed onto the powder mixture in the fluid-bed granulator and the obtained granulate was then dried in a fluid-bed dryer at an inlet temperature of 70°C. The dried granulate was passed through an 18-mesh sieve and mixed with maize starch (30 g) and hydrogenated vegetable oil (3 g) in a biconic mixer.

The mixture to be tabletted (the granulate with admixed maize starch and hydrogenated castor oil) was compressed into tablets, each containing 5 mg of donepezil hydrochloride. The average weight of the tablets was 140 mg.

Example 3

Preparation of tablets

Donepezil (30 g) was dispersed in purified water (320 g). During a fast stirring of the dispersion, concentrated hydrochloric acid (6 ml) was slowly added. A mixture of lactose monohydrate (818 g), crospovidone (40 g) and povidone (25 g) was passed through a 30-mesh sieve and subsequently mixed in a fluid-bed granulator.

The aqueous solution of donepezil hydrochloride to be granulated was sprayed onto the powder mixture in the fluid-bed granulator and the obtained granulate was then dried in a fluid-bed dryer at an inlet temperature of 60°C. The dried granulate was passed through an 18-mesh sieve and mixed with magnesium stearate (5 g) in a biconic mixer.

The mixture to be tabletted (the granulate with admixed magnesium stearate) was compressed into tablets, each containing 10 mg of donepezil hydrochloride. The average weight of the tablets was 280 mg.

Example 4

Preparation of cores

Donepezil (34 g) was dispersed in purified water (360 g). During a fast stirring of the dispersion, concentrated hydrochloric acid (7 ml) was slowly added. Lactose monohydrate (605 g), microcrystalline cellulose (231 g), maize starch (50 g) and hydroxypropylcellulose (30 g) were passed through a 30-mesh sieve and subsequently mixed in a fluid-bed granulator.

The aqueous solution of donepezil hydrochloride (pH = 4.5) to be granulated was sprayed onto the powder mixture in the fluid-bed granulator and the obtained granulate was then dried in a fluid-bed dryer at an inlet temperature of 70°C. The dried granulate was passed through an 18-mesh sieve and admixed with maize starch (50 g) and magnesium stearate (5 g) in a biconic mixer.

The mixture to be tableted (the granulate with admixed maize starch and magnesium stearate) was compressed into cores, each containing 10 mg of donepezil hydrochloride. The average weight of the cores was 280 mg.

Preparation of film-coated tablets

The obtained cores were coated with a conventional ready-to-make mixture for the preparation of a film-coating suspension containing hydroxypropylmethylcellulose, macrogol 400, iron oxide yellow and titanium dioxide, until the average weight of the film coated tablets was 288 mg.

The pH value of film coated tablets dispersed in purified water was 6.4.

Example 5

Preparation of tablets

Donepezil (300 g) was dispersed in purified water (300 g). During a fast stirring of the dispersion 0.5 M hydrochloric acid (520 ml) was slowly added. The aqueous solution of donepezil hydrochloride was spray-dried on a mini spray-dryer Büchi 190.

Amorphous donepezil hydrochloride (100 g) was dissolved in purified water (1000 ml). Hydroxypropylcellulose (85 g), lactose monohydrate (1680 g), microcrystalline cellulose (640 g) and maize starch (140 g) were passed through a 30-mesh sieve.

The aqueous solution of donepezil hydrochloride to be granulated was sprayed onto the powder mixture in a fluid-bed granulator and the obtained granulate was then dried in a fluid-bed dryer at an inlet temperature of 65°C. The dried granulate was passed through an 18-mesh sieve and admixed with maize starch (140 g) and magnesium stearate (15 g) in a biconic mixer.

The mixture to be tableted (the granulate with admixed maize starch and magnesium stearate) was compressed into tablets, each containing 5 mg of donepezil hydrochloride. The average weight of the tablets was 140 mg.

Example 6

Preparation of cores

Donepezil (300 g) was dispersed in purified water (300 g). During a fast stirring of the dispersion, 0.5 M hydrochloric acid (520 ml) was slowly added. Separately, povidone (329 g) was dissolved in purified water (1200 ml). Both solutions were mixed together in such a manner that the aqueous solution of donepezil hydrochloride was added to

the solution of povidone. The aqueous solution obtained was spray-dried on a mini spray-dryer Büchi 190.

Amorphous donepezil hydrochloride (50 g) stabilised with povidone (50 g) was dissolved in purified water (1000 ml). Hydroxypropylcellulose (42 g), lactose monohydrate (790 g), microcrystalline cellulose (320 g) and maize starch (70 g) were passed through a 30-mesh sieve.

The aqueous solution of donepezil hydrochloride to be granulated was sprayed onto the powder mixture in a fluid-bed granulator and the obtained granulate was then dried in a fluid-bed dryer at an inlet temperature of 65°C. The dried granulate was passed through an 18-mesh sieve and admixed with maize starch (70 g) and magnesium stearate (8 g) in a biconic mixer.

The mixture to be tabletted (the granulate with admixed maize starch and magnesium stearate) was compressed into cores, each containing 5 mg of donepezil hydrochloride. The average weight of the cores was 140 mg.

Preparation of film coated tablets

The obtained cores were coated with a conventional ready-to-make mixture for the preparation of a film-coating suspension containing hydroxypropylmethylcellulose, macrogol 400 and titanium dioxide, until the average weight of the film coated tablets was 144 mg.

Claims

1. Pharmaceutical composition with donepezil hydrochloride containing an amorphous form or stabilised amorphous form thereof, characterized in that it is manufactured by preparing donepezil hydrochloride *in situ* and by adding a crystallization inhibitor.
2. Pharmaceutical composition according to claim 1, characterized in that the crystallization inhibitor is selected from at least one of cellulose derivatives, polyvinylpyrrolidone and derivatives thereof, xanthan gums, pectins, alginates, tragacanth and derivatives, gum arabic and derivatives, carrageenans, agar and derivatives, polysaccharides from microbiological sources, arabinogalactanes, galactomannans, dextrans.
3. Pharmaceutical composition according to claims 1 or 2, characterized in that the crystallization inhibitor is added in an amount from 0.0001g to 5.0 g for 1 g of donepezil hydrochloride.
4. A process for the preparation of a pharmaceutical composition according to any of the claims 1 to 3 comprising the steps:
 - a) dispersing donepezil in a pharmaceutically acceptable solvent and adding a hydrochloric acid solution to the dispersion,
or *vice versa*, adding donepezil to a hydrochloric acid solution in a pharmaceutically acceptable solvent, and
 - b) loading the obtained solution onto a mixture of pharmaceutically acceptable carriers.

5. A process according to claim 4, characterized in that the crystallization inhibitor is added either to the solution obtained or to the mixture of pharmaceutically acceptable excipients.
6. A process according to claim 4, characterized in that the molar ratio of donepezil to hydrochloric acid is 1 to 0.5–5.
7. A process according to claim 4, characterized in that pharmaceutically acceptable solvents are water, acetone, alcohols, a mixture of water with water-miscible solvents.
8. A process for the preparation of an amorphous form of donepezil hydrochloride, characterized in that donepezil hydrochloride is dissolved in a pharmaceutically acceptable solvent or donepezil hydrochloride is prepared *in situ* and the obtained solution is spray-dried.
9. A use of donepezil hydrochloride prepared according to the process of claim 8 for the preparation of a pharmaceutical composition, characterized in that donepezil hydrochloride is dissolved in a pharmaceutically acceptable solvent and the obtained solution is loaded onto a mixture of pharmaceutically acceptable carriers or that donepezyl hydrochloride is directly loaded onto the pharmaceutical composition.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/445 1P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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